Medscape EDUCATION

Expert Perspectives on Clinical Cases in the Management of Myasthenia Gravis

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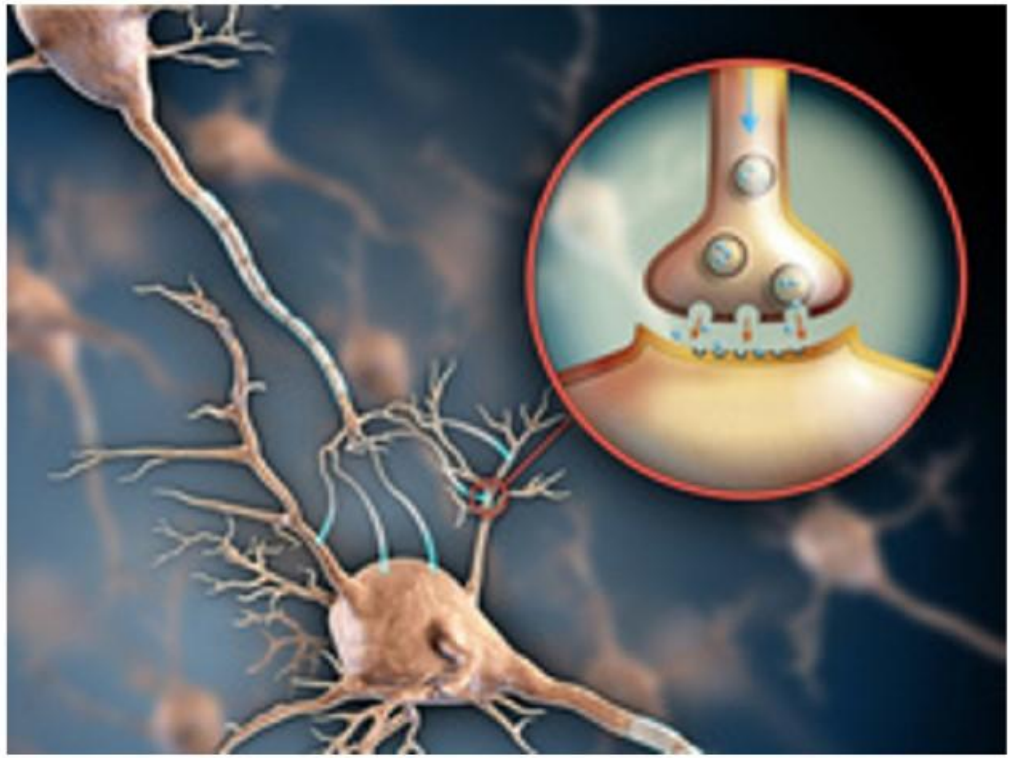
gMG Epidemiology

Rare, chronic autoimmune NMJ disorder; most patients progress to gMG within 2 y of diagnosis[a]

- NMJ disorders are rare[b]
- Of the acquired NMJ disorders, MG is the most common[c]
- Incidence estimated at 0.3 to 2.8 per 100,000[d]
- Worldwide prevalence estimated at 700,000[d]
- Mortality rate: 0.06 to 0.89 per million person-years[d]

a. Grob D, et al. *Muscle Nerve*. 2008;37:141-149.; b. Deenen JC, et al. *J Neuromuscul Dis*. 2015;2:73-85; c. Gilhus NE. *Expert Rev Neurother*. 2009;9:351-358; d. Carr AS, et al. *BMC Neurol*. 2010;10:46.

Program Overview



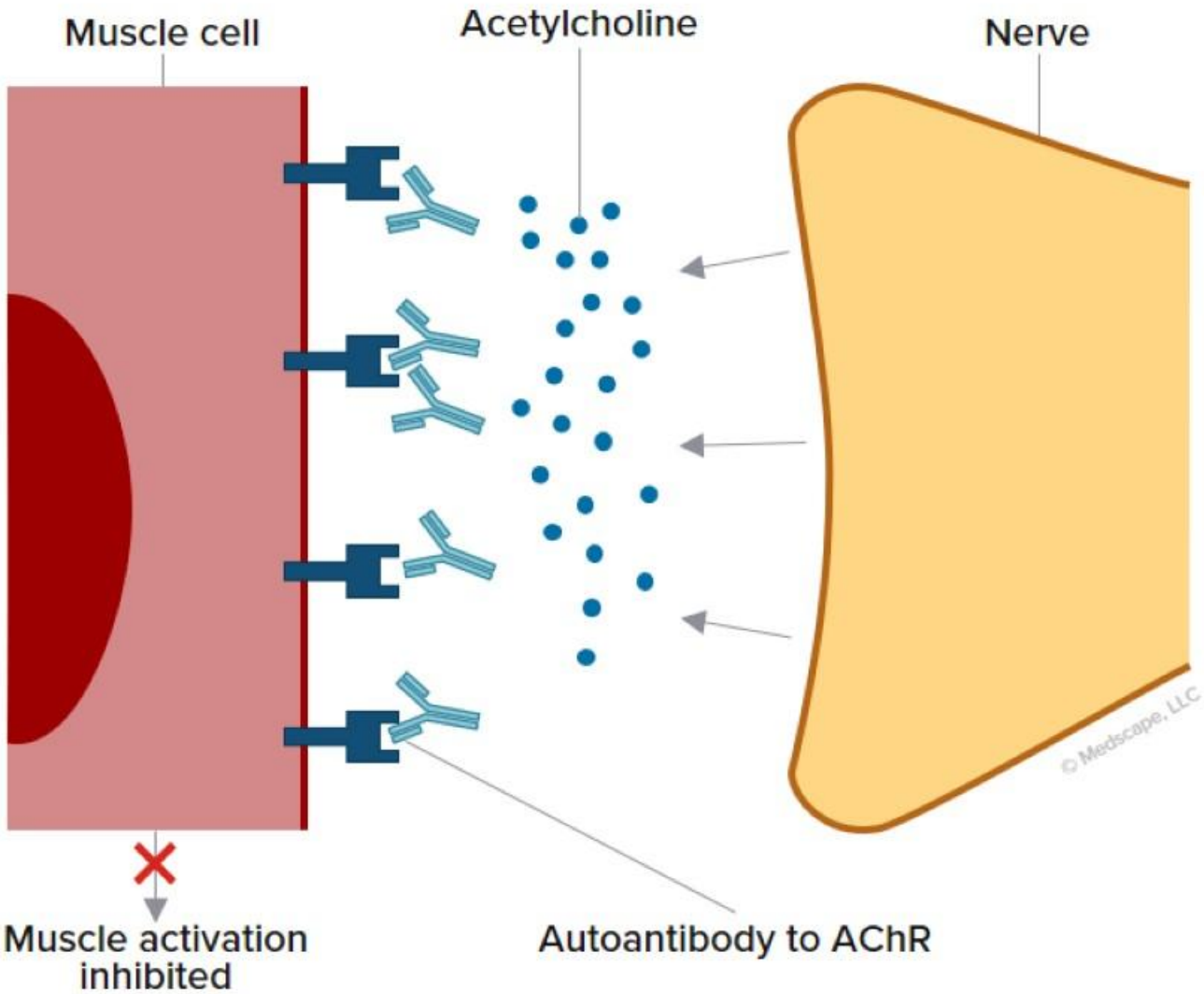
In this program, we will discuss the following:

- Pathophysiology, presentation, and diagnosis
- Treatment of gMG
- Impact of Ab status and treatment considerations
  - Anti-AChR Ab+
  - Anti-MuSK Ab+
  - Seronegative

gMG Pathophysiology

Autoimmune NMJ Disorder

Characteristic muscle weakness is caused by pathogenic autoantibodies that bind to components of the NMJ[a]



a. Verschuuren JJ, et al. *Autoimmun Rev.* 2013;12:918-923.

gMG Pathophysiology (cont)

Autoimmune NMJ Disorder

Characteristic muscle weakness is caused by pathogenic autoantibodies that bind to components of the NMJ[a]

AChR Ab+

~85% due to the presence of Abs to AChR[b]

Disease pathology is by cross-linking, functional blockade, and complement-mediated damage (IgG1, IgG3)[c]

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Other Proteins

Abs to other proteins can also impair signaling at the NMJ[d]

- MuSK (MuSK, IgG4)
- LRPR (LRP4, IgG1)
- Others

a. Verschuuren JJ, et al. *Autoimmun Rev*. 2013;12:918-923; b. Meriggioli MN, et al. *Lancet Neurol*. 2009;8:475-490; c. Fichtner ML, et al. *Front Immunol*. 2020;11:776; d. Gilhus NE, et al. *Lancet Neurol*. 2015;14:1023-1036.

Clinical Presentation

Clinical hallmark: fluctuating, pronounced, fatigable weakness limited to the voluntary muscles[a]

a. Juel VC, et al. *Orphanet J Rare Dis*. 2007;2:44.

Clinical Presentation (cont)

Clinical hallmark: fluctuating, pronounced, fatigable weakness limited to the voluntary muscles[a]

Ocular (ptosis, diplopia): up to 85%[b]

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Clinical Presentation (cont)

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Bulbar (dysarthria, dysphagia): 15% to 20%[c]

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Extremity weakness (usually proximal)[c]

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Extremity weakness (usually proximal)[c]

Distal extremity involvement is rare[c]

Respiratory involvement is rare[c]

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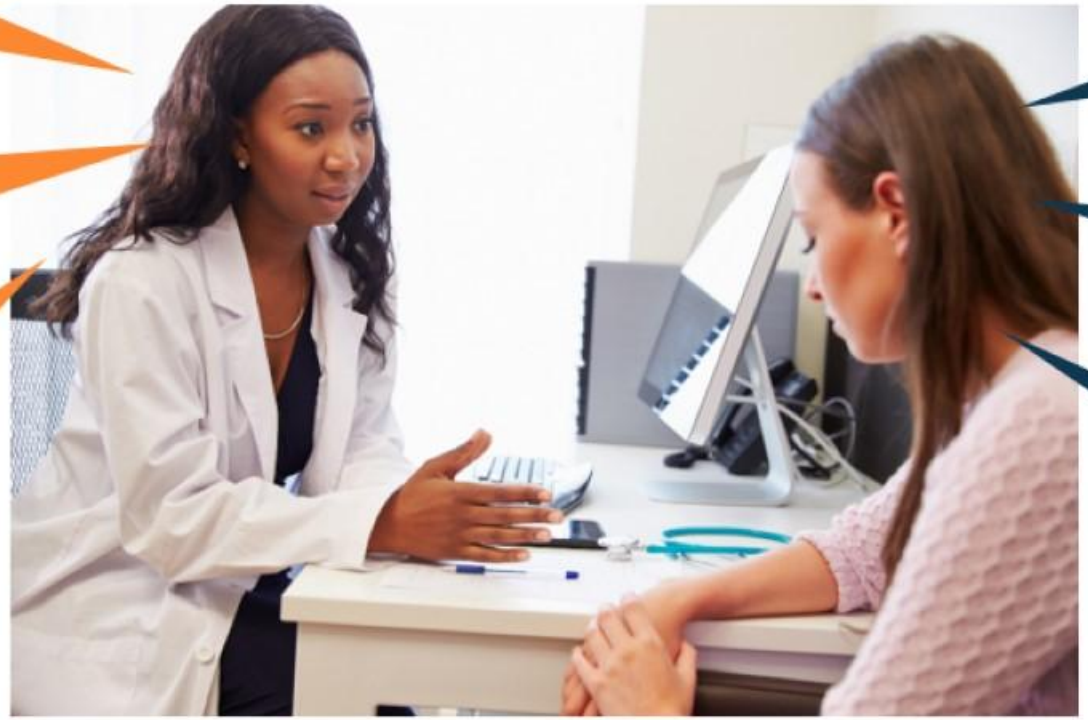
Diagnosis
History of Fatigable Weakness

When patients present with symptoms suggestive of gMG, differentiate from generalized weakness or fatigue

How do you feel first thing in the morning?

Does your weakness improve after rest?

How are your symptoms after repetitive activities?



My symptoms are better in the morning.

My weakness improves after a nap.

My jaw fatigue worsens the longer I chew.

Juel VC, et al. *Orphanet J Rare Dis*. 2007;2:44.

Diagnostic Tests

Abs

Diagnostic assays specific for pathogenic Abs: AChR, MuSK, LPR4, others

Ice Pack Test

Ophthalmologist may use ice pack test for primary ocular presentation

EMG/NCS

Repetitive stimulation
SFEMG

Chest CT Scan

Evaluate for thymoma

Pasnoor M, et al. *Neurol Clin*. 2018;36:261-274.

Diagnosis and Ab Status

AChR Ab+[a]

Positive AChR

Repetitive stimulation and SFEMG useful

MuSK Ab+[b]

Positive MuSK

Repetitive stimulation and SFEMG sometimes useful

a. Pasnoor M, et al. *Neurol Clin*. 2018;36:261-274; b. Meriggioli MN, et al. *Expert Rev Clin Immunol*. 2012;8:427-438.

Diagnosis and Ab Status (cont)

AChR Ab+[a]

Positive AChR

Repetitive stimulation and SFEMG useful

MuSK Ab+[b]

Positive MuSK

Repetitive stimulation and SFEMG sometimes useful

Detecting circulating anti-AChR or anti-MuSK Abs provides an important confirmation of clinical diagnosis and allows specific treatment[b]

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Diagnosis and Ab Status (cont)

AChR Ab+[a]

Positive AChR

Repetitive stimulation and SFEMG useful

MuSK Ab+[b]

Positive MuSK

Repetitive stimulation and SFEMG sometimes useful

Seronegative[c]

Negative for AChR, MuSK, and LRP4

Repetitive stimulation and SFEMG very useful

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Why Are Some Patients Seronegative?

Autoantibodies not detected in ~ 10% of patients with MG[a]

Seronegative MG:

- Not immunosuppressed
- Lack of autoantibodies at presentation at follow-up of ≥ 12 mo
- Clinical and electrodiagnostic features consistent with MG

Lack of autoantibodies due to:

- Undetectable levels
- Epitopes not detected by assay
- Unknown targets
- Falsely seronegative
- Congenital MG
- Retest at 12 mo

Chan KH, et al. *Muscle Nerve*. 2007;36:651-658.

AChR Ab+ gMG Tx
A Case-Based Perspective

Sex: Male

Age	68 y
History	▪ Macular degeneration ▪ Initial symptoms: ptosis and double vision
AChR antibody test	▪ Positive
Initial tx	▪ Pyridostigmine 60 mg once per day

MG diagnosis confirmed: AChR Ab+

Initial symptoms

- Ptosis, double vision

Initial tx

- AChEI

Duration of symptom control

- 6 mo

AChR Ab+ gMG Tx

A Case-Based Perspective: Second-line Tx, AChR Ab+

Sex: Male

History	▪ AChR Ab+ gMG
Presentation at 6 mo	▪ Slurred speech and trouble swallowing
	▪ Negative workup for stroke ▪ CT scan negative for thymoma
Workup	▪ MG exacerbation
Second-line Tx	▪ Pyridostigmine 60 mg once per day ▪ Prednisone 60 mg

Symptoms at 6 mo

- Slurred speech
- Trouble swallowing

Second-line tx

- AChEI
- Corticosteroid

AChR Ab+ gMG Tx

A Case-Based Perspective: Third-line Tx, AChR Ab+

Sex: Male

History	▪ AChR Ab+ gMG
Tx	▪ Mycophenolate 500 mg in the morning and 1000 mg at night ▪ Pyridostigmine 60 mg 3 times daily ▪ Prednisone 40 mg daily
Presentation at worst	▪ Slurred speech and trouble swallowing ▪ Ptosis and double vision

Symptoms at 6 mo

- Slurred speech
- Trouble swallowing

Treatment

- AChEI
- ± Corticosteroid
- Nonsteroidal IST

AChR Ab+ gMG Tx
A Case-Based Perspective: Persistent Symptoms

Sex: Male

History	▪ AChR Ab+ gMG
Third-line tx	▪ Mycophenolate 500 mg in the morning and 1000 mg at night ▪ Pyridostigmine 60 mg 3 times daily ▪ Prednisone 40 mg daily
Steroid taper	▪ Symptoms worsened

Symptoms at worst

- **Ptosis**
- **Fatigue with chewing**
- **Double vision**
- **Slurred speech**
- **Trouble swallowing**
- **Generalized fatigue**
- **Tx AEs**

Patient referred to specialist

gMG Tx Considerations

Patients with uncontrolled gMG cycle through multiple lines of therapy to achieve disease stability or better QoL

- **2020 Updated consensus tx statements based on new clinical trial data published after 2016**[a,b]
- **gMG therapies are off-label except acetylcholinesterase inhibitors and complement inhibition with eculizumab**[c,d,e]
- **Aim of tx is to induce remission or minimal manifestations with manageable medication AEs**[a]
- **Ab status is included in the consensus guidance statements and is important for diagnosis and tx decision-making**[a,b]

a. Sanders DB, et al. *Neurology*. 2016;87:419-425; b. Narayanaswami P, et al. *Neurology*. 2021;96:114-122; c. Soliris (eculizumab) [PI]. 2020; d. Pyridostigmine bromide [PI]. 2003; e. Mytelase (ambenoium chloride) [PI]. 2003.

International Consensus Guidance

VIEWS & REVIEWS

International consensus guidance for management of myasthenia gravis

Executive summary

OPEN

Donald B. Sanders, MD*
Gil I. Wolfe, MD*
Michael Benatar, MD, PhD
Amelia Evoli, MD
Nils E. Gilhus, MD
Isabel Illa, MD
Nancy Kuntz, MD
Janice M. Massey, MD
Arthur Melms, MD
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Jacqueline Palace, BM, DM
David P. Richman, MD
Jan Verschuuren, MD
Pushpa Narayanaswami, MBBS, DM*

ABSTRACT

Objective: To develop formal consensus-based guidance for the management of myasthenia gravis (MG).

Methods: In October 2013, the Myasthenia Gravis Foundation of America appointed a Task Force to develop treatment guidance for MG, and a panel of 15 international experts was convened. The RAND/UCLA appropriateness methodology was used to develop consensus guidance statements. Definitions were developed for goals of treatment, minimal manifestations, remission, ocular MG, impending crisis, crisis, and refractory MG. An in-person panel meeting then determined 7 treatment topics to be addressed. Initial guidance statements were developed from literature summaries. Three rounds of anonymous e-mail votes were used to attain consensus on guidance statements modified on the basis of panel input.

Results: Guidance statements were developed for symptomatic and immunosuppressive treatments, IV immunoglobulin and plasma exchange, management of impending and manifest myasthenic crisis, thymectomy, juvenile MG, MG associated with antibodies to muscle-specific tyrosine kinase, and MG in pregnancy.

Conclusion: This is an international formal consensus of MG experts intended to be a guide for clinicians caring for patients with MG worldwide. *Neurology*® 2016;87:419-425

Sanders DB, et al. *Neurology*. 2016;87:419-425.

International Consensus Guidance Updated in 2020

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VIEWS & REVIEWS | OPEN ACCESS | LEVEL OF RECOMMENDATION

International Consensus Guidance for Management of Myasthenia Gravis

2020 Update

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Neurology® 2021;96:114-122. doi:10.1212/WNL.0000000000011124

Abstract

Objective

To update the 2016 formal consensus-based guidance for the management of myasthenia gravis (MG) based on the latest evidence in the literature.

Methods

In October 2013, the Myasthenia Gravis Foundation of America appointed a Task Force to develop treatment guidance for MG, and a panel of 15 international experts was convened. The RAND/UCLA appropriateness method was used to develop consensus recommendations pertaining to 7 treatment topics. In February 2019, the international panel was reconvened with the addition of one member to represent South America. All previous recommendations were reviewed for currency, and new consensus recommendations were developed on topics that required inclusion or updates based on the recent literature. Up to 3 rounds of anonymous e-mail votes were used to reach consensus, with modifications to recommendations between rounds based on the panel input. A simple majority vote (80% of panel members voting "yes") was used to approve minor changes in grammar and syntax to improve clarity.

a. Sanders DB, et al. *Neurology*. 2016;87:419-425. b. Narayanaswami P, et al. *Neurology*. 2021;96:114-122.

Consensus Tx Guidance

2016 Guidance Statements[a]

- Thymectomy
- AChEIs (pyridostigmine)
- Corticosteroids
- Nonsteroidal ISTs
- IVIG or PLEX
- Other ISTs (off-label rituximab, methotrexate)

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Consensus Tx Guidance (cont)

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2020 Guidance Statements

- *New*
  - Complement inhibitor (eculizumab)[b,c]
- *Updated*
  - Thymectomy[b]
  - Other ISTs (off-label rituximab, methotrexate)[a,b]
- *No change*
  - AChEIs[a,b]
  - Corticosteroids: no change[a,b]
  - Nonsteroidal ISTs[a,b]
  - IVIG or PLEX[a,b]

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gMG Tx Considerations (cont)

Patients with uncontrolled gMG cycle through multiple lines of therapy to achieve disease stability or better QoL

- **2020 Updated consensus tx statements based on new clinical trial data published after 2016**[a,b]
- **gMG therapies are off-label except acetylcholinesterase inhibitors and complement inhibition with eculizumab**[c,d,e]
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MGTX RCT and Long-Term Data for Thymectomy AChR Ab+ gMG

Study Design

- 126 patients with AChR Ab+ gMG randomized to thymectomy + prednisone vs prednisone alone[a]

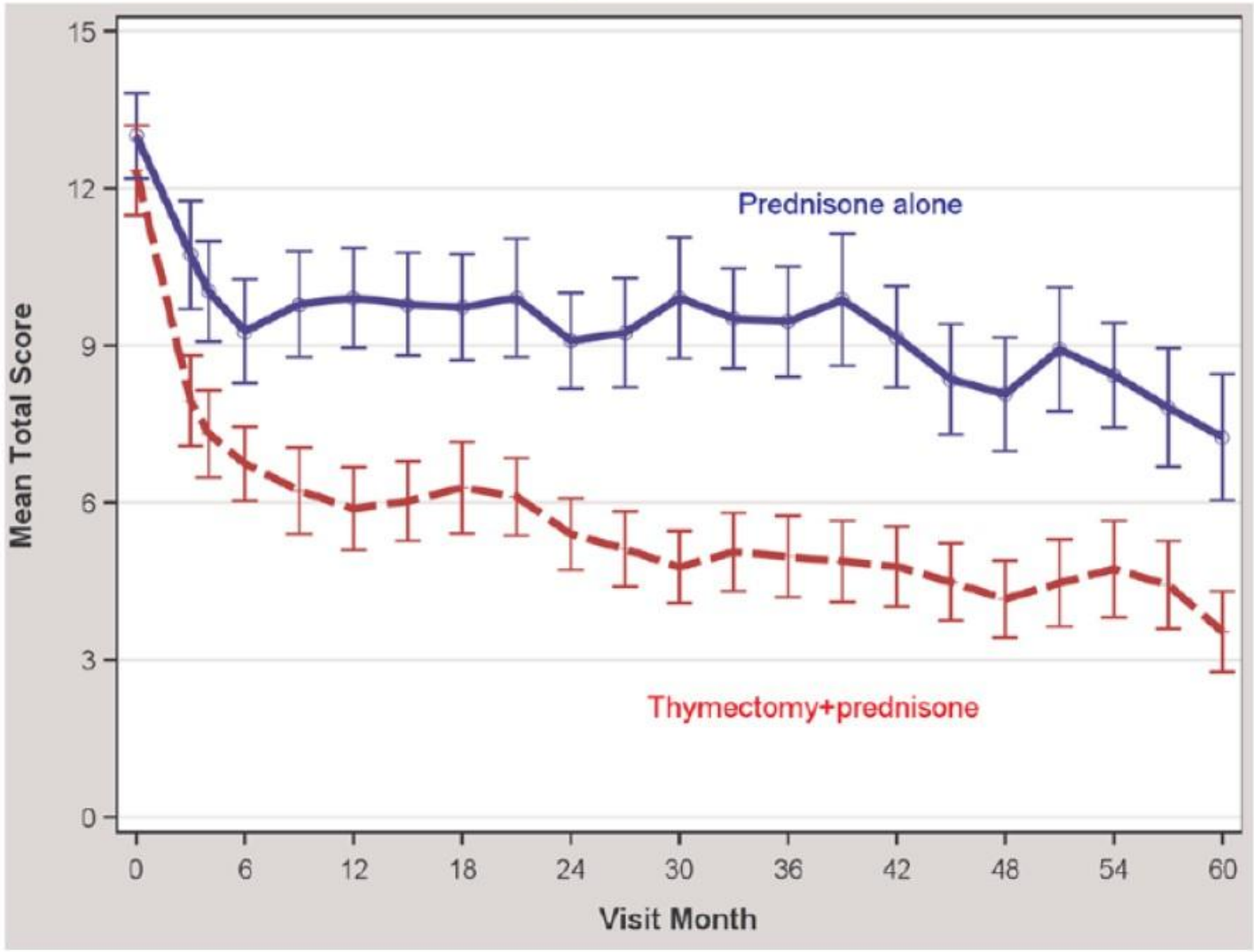
Study Findings

- Thymectomy + prednisone group had a lower time-weighted average QMG score (6.15 vs 8.99; $P < .001$)[a]
- Thymectomy + prednisone group had a lower average requirement for alternate-day prednisone (44 mg vs 60 mg; $P < .001$)[a]
- At age ≥ 50 y, no significant difference between tx groups in post hoc analysis[a]

Long-Term Data

- 5-y data provide more evidence to support thymectomy in AChR Ab+ gMG[b]

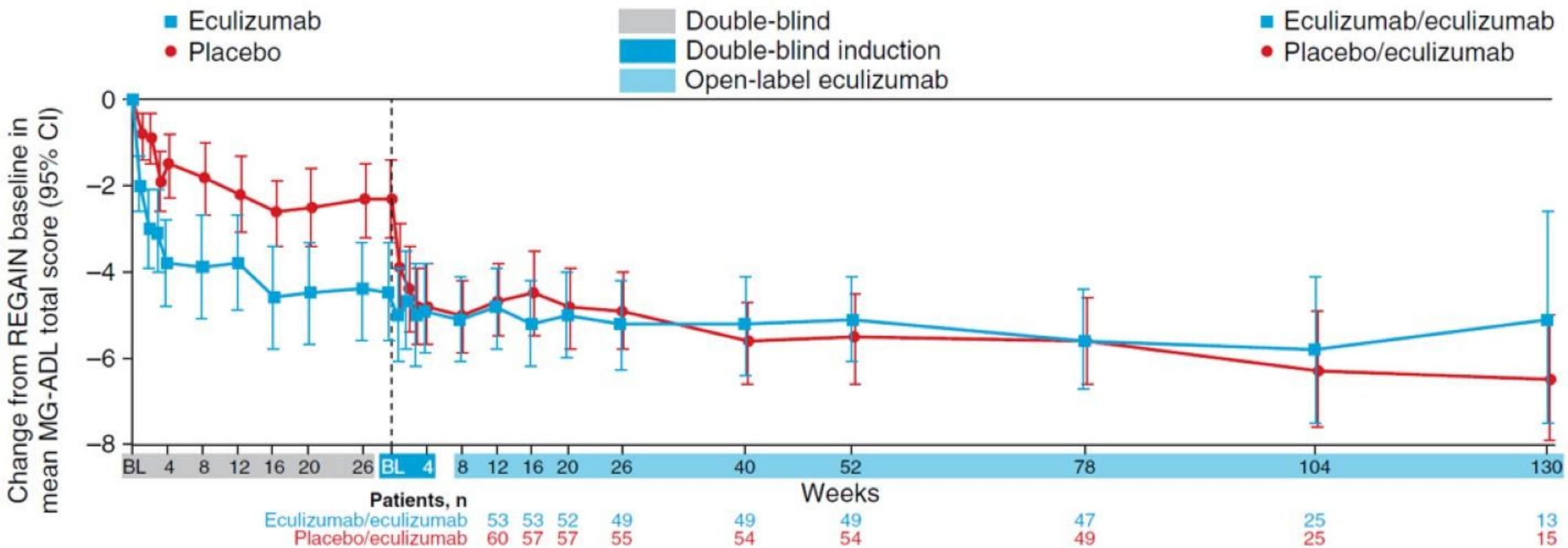
QMG Score by Tx Group Over 5 y[b]



a. Wolf GI, et al. *N Engl J Med*. 2016;375:511-522; b. Wolfe GI, et al. *Lancet Neurol*. 2019;18:259-268.

REGAIN RCT and Extension Study in AChR Ab+ Refractory gMG

Safety profile during extension study was consistent with REGAIN. Improvements with eculizumab in ADL, muscle strength, functional ability, and QoL were maintained through 3 y.



Howard JF Jr, et al. *Lancet Neurol*. 2017;16:976-986; Muppidi S, et al. *Muscle Nerve*. 2019;60:14-24.

Rituximab Data Considered in 2020 Guideline Update

- **Uncertain efficacy in refractory AChR Ab+, option for IST failure or intolerance[a]**
- **No change from 2016 guidance statement for off-label rituximab in MuSK antibody-positive gMG[a,b]**

Study Population	Trial Design	Outcomes Summary
AChR Ab+	BeatMG, phase 2 RCT[c]	No significant steroid-sparing effect vs placebo[a,c]
Refractory AChR Ab+, MuSK Ab+, or seronegative	Prospective, open label[d]	MMT score improvement[d]
AChR Ab+ or MuSK Ab+	Retrospective[e]	25% achieved MM at median of 20 mo[e]
Refractory AChR Ab+, MuSK Ab+, or seronegative	Prospective, open label[f]	Significant improvement from BL[f]
AChR Ab+, MuSK Ab+, seronegative	Single center, retrospective[g]	PIS improved 43% at 6 mo[g]
MuSK Ab+	Multicenter, blinded, prospective review[h]	58% achieved MM status[h]

a. Narayanaswami P, et al. *Neurology*. 2021;96:114-122; b. Sanders DB, et al. *Neurology*. 2016;87:419-425; c. Nowak RJ, et al. *Neurology*. 2018;90:e2182-e2194; d. Beecher G, et al. *Muscle Nerve*. 2018;58:452-455; e. Topakian R, et al. *J Neurol*. 2019;266:699-706; f. Anderson D, et al. *Ann Clin Translational Neurol*. 2016;3:552-555; g. Afanasiev V, et al. *Neuromuscul Disord*. 2017;27:251-258; h. Hehir MK, et al. *Neurology*. 2017;89:1069-1077.

gMG Tx Considerations (cont)

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Tx and Ab Status

AChR Ab+

- Thymectomy[a]

- AChEI[b]
- Corticosteroids[b]
- IST[b]

- IVIG and PLEX[b]

- Refractory:
  - Eculizumab[a,c]

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Tx and Ab Status (cont)

AChR Ab+

- Thymectomy[a]
- AChEI[b]
- Corticosteroids[b]
- IST[b]
- IVIG and PLEX[b]
- Refractory:
  - Eculizumab[a,c]

MuSK Ab+

- Thymectomy not beneficial[d]
- Less response to AChEI[b,e]
- Corticosteroids[b]
- IST[b]
- Less response to IVIG[b,d]
- PLEX[b,f]
- Refractory:
  - Off-label rituximab[b]

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Tx and Ab Status (cont)

AChR Ab+

- Thymectomy[a]
- AChEI[b]
- Corticosteroids[b]
- IST[b]
- IVIG and PLEX[b]
- Refractory:
  - Eculizumab[a,c]

MuSK Ab+

- Thymectomy not beneficial[d]
- Less response to AChEI[b,e]
- Corticosteroids[b]
- IST[b]
- Less response to IVIG[b,d]
- PLEX[b,f]
- Refractory:
  - Off-label rituximab[b]

Seronegative

- Less need for thymectomy[g]
- Response to AChEI, corticosteroids, and IST similar to response to AChR Ab+[g]

a. Narayanaswami P, et al. *Neurology*. 2021;96:114-122; b. Sanders DB, et al. *Neurology*. 2016;87:419-425; c. Soliris (eculizumab) [PI]. 2020; d. Sanders DB, et al. *Neurology*. 2003;60:1978-1980; e. Huda S, et al. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e357; f. Romi F, et al. *Eur J Neurol*. 2005;12:413-418; g. Guptill JT, et al. *Curr Opin Neurol*. 2010;23:530-535.

Tx Considerations
Onset of Action

Tx	Onset of Action
AChEI: pyridostigmine	15 to 30 min
Corticosteroids	2 to 4 wk
IST: azathioprine	12 to 18 mo
IST: mycophenolate mofetil	3 to 6 mo
Thymectomy	6 to 12 mo
IVIG	1 to 2 wk
PLEX	1 to 2 exchanges
Rituximab	1 to 3 mo
Eculizumab	2 to 4 wk

How rapidly is improvement needed?

Farmakidis C, et al. *Neurol Clin*. 2018;36:311-337.

Refractory AChR Ab+ gMG

Distinct subset of patients with aggressive and difficult-to-treat gMG[a]

- **Patients with treatment-refractory gMG have worse QoL scores[a]**
- **~ 50% of patients chronically have MG-ADL scores > 6[b]**
- **~ 50% of patients have difficulty attaining satisfactory disease control in the first 3 y after diagnosis despite aggressive treatment[c]**

a. Schneider-Gold C, et al. *Ther Adv Neurol Disord.* 2019;12:1756286419832242. b. Boscoe AN, et al. *J Clin Neuromuscul Disord.* 2019;20:173-181; c. Baggi F et al. *Neurology.* 2013;80:188-195.

Emerging Therapies

C5 Inhibitors	▪ Eculizumab in seronegative gMG[a]
New C5 Inhibitors	▪ Ravulizumab in gMG unspecified[b] ▪ Zilucoplan in AChR+ gMG[c]
FcRn Blockers	▪ Efgartigimod[d]

a. Datta S, et al. *J Neuromuscul Dis*. 2020;7:269-277; b. Bernuy-Guevara C, et al. *Biomedicines*. 2020;8:355; c. Howard JF Jr, et al. *JAMA Neurol*. 2020;77:582-592; d. Howard JF Jr, et al. *Neurology*. 2019;92:e2661-e2673.

Conclusion

- The 2020 update to consensus guidelines based on clinical trial data are an important reference
- Consider complicated patient referral to high-volume specialist
- Important to identify Ab status of patient and manage accordingly
- Important to distinguish true seronegative from lack of autoantibodies due to treatment or other reasons

Abbreviations

Ab = antibody

Ab+ = antibody positive

AChEI = acetylcholinesterase inhibitor

AChR = acetylcholine receptor

ADL = activities of daily living

AE = adverse effect

BL = baseline

C5 = component 5

CT = computed tomography

EMG = electromyogram, electromyography

FcRn = neonatal crystallizable fragment receptor

FDA = Food and Drug Administration

gMG = generalized myasthenia gravis

Abbreviations (cont)

Ig = immunoglobulin

IST = immunosuppressive treatment

IVIG = intravenous immunoglobulin

LRP4 = low-density lipoprotein receptor-related protein 4

MG = myasthenia gravis

MM = minimal manifestation

MMT = manual muscle testing

MuSK = muscle-specific kinase

NCS = nerve conduction study

NMJ= neuromuscular junction

PIS = postintervention status

PLEX = plasma exchange

QMG = Quantitative Myasthenia Gravis

Abbreviations (cont)

QoL = quality of life

RCT = randomized controlled trial

SFEMG = single-fiber electromyography

Tx = treatment